A Novel Wearable Device for Motor Recovery of Hand Function in Chronic Stroke Survivors

Supriyo Choudhury, MD[1], Ravi Singh, MSc[1], A. Shobhana, MD[1], Dwaipayan Sen, MBBS, FRCP[1], Sidharth Shankar Anand, MD, DM[1], Shantanu Shubham, MD, DM[1], Suparna Gangopadhyay[2], MD, Mark R. Baker, PhD, FRCP[3,4], Hrishikesh Kumar, MD, DM[1], Stuart N. Baker, PhD[3]

1: Department of Neurology and RGC Research Centre, Institute of Neurosciences, Kolkata, India
2: Department of Neurorehabilitation, Institute of Neurosciences, Kolkata, India
3: Institute of Neurosciences, Newcastle University, Newcastle upon Tyne, NE2 4HH, UK
4: Departments of Neurology and Clinical Neurophysiology, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, UK

Corresponding author:
Prof Stuart Baker,
Institute of Neurosciences,
Henry Wellcome Building,
Medical School,
Newcastle upon Tyne,
NE2 4HH.
Email: stuart.baker@ncl.ac.uk
Phone: +44 191 284 8397

Facebook: @newcastleuniversity
Twitter: @UniofNewcastle
Facebook: @neurokolkata

Cover title: Wearable-Device for Hand-Function Recovery
Figures: 2
Tables: 2
Key words: stimulation, plasticity, rehabilitation, ARAT, upper limb, hand
Subject Term: Neurostimulation
Number of words for abstract: 250
Number of words for manuscript: 3689

Abstract

Background: In monkey, reticulospinal connections to hand and forearm muscles are spontaneously strengthened following corticospinal lesion, likely contributing to recovery of function. In healthy humans, pairing auditory clicks with electrical stimulation of a muscle induces plastic changes in motor pathways (probably including the reticulospinal tract), with features reminiscent of spike-timing dependent plasticity. In this study, we tested whether pairing clicks with muscle stimulation could improve hand function in chronic stroke survivors.

Methods: Clicks were delivered via a miniature earpiece; transcutaneous electrical stimuli at motor threshold targeted forearm extensor muscles. A wearable electronic device (WD) allowed patients to receive stimulation at home while performing normal daily activities. Ninety-five patients >6 months post-stroke were randomised to three groups: WD with shock paired 12 ms before click; WD with clicks and shocks delivered independently; standard care. Those allocated to the device used it for at least 4 hours per day, every day for 4 weeks. Upper limb function was assessed at baseline, and weeks 2, 4 and 8, using the Action Research Arm Test (ARAT) which has four sub-domains (Grasp, Grip, Pinch and Gross).

Results: Severity across the three groups was comparable at baseline. Only the Paired Stimulation Group showed significant improvement in total ARAT (median baseline: 7.5; week 8: 11.5; p=0.019) and the Grasp sub-score (median baseline: 1, week 8: 4; p=0.004).

Conclusion: A wearable device delivering paired clicks and shocks over four weeks can produce a small but significant improvement in upper limb function in stroke survivors.

Trial registration - CTRI/2018/03/012628.

Introduction

Stroke incidence has more than doubled in low- and middle income countries in the last three decades[1]. Among survivors, 30-66% lose the upper limb functions[2,3] fundamental to activities of daily living. Rehabilitating hand movements is thus essential to restore independence. Standard therapist-led approaches can be effective, but access to such resources in low- and middle-income countries such as India is extremely limited[4]. Even in the UK, input from a therapist is rare beyond six months post-stroke[5]; half of UK stroke survivors consider available rehabilitation services as suboptimal[6]. Effective solutions that complement conventional approaches and reduce the contact time required from therapists are clearly needed if the outlook for stroke survivors globally is to improve.

In primates such as humans, motor control is dominated by the corticospinal tract, which is responsible for our sophisticated motor repertoire including fine control of independent finger movements. Other pathways such as the reticulospinal tract also contribute, even to the control of the hand[7]. The reticulospinal tract (RST) becomes especially important during motor recovery after corticospinal damage such as following stroke, when reticulospinal connections strengthen[8,9], partly subserving recovery[10], but also limiting the quality of recovered movements[8,11]. Non-invasive methods to activate and manipulate the RST are limited, but in monkey we have shown that loud auditory clicks produce a robust burst of firing in reticular cells[12]. We previously developed a prototype wearable device capable of continually delivering clicks paired with transcutaneous electrical stimulation of a muscle while a subject went about their normal daily activities[13]. In healthy human volunteers, this device induced long term changes in motor output; the direction of changes (facilitation vs suppression) depended on the click-shock interval, as expected if the stimuli induced spike-timing dependent plasticity[14] in the RST. We therefore hypothesized that this paired stimulation protocol could further strengthen RST connections in patients recovering from stroke, yielding improvements in upper limb function.

Aims

Supported by these recent observations, we developed the wearable device further to be suitable for patient use, with the aim of delivering a domiciliary aid to long term rehabilitation. Here we present the results of a clinical trial exploring the feasibility, safety and efficacy of this device in stroke survivors with upper limb impairment.

Methods

Subjects

In this observer-blind, randomised, parallel-group clinical trial, consecutive stroke patients attending the neurology out-patient department and/or the stroke clinic of a regional neurosciences hospital in Kolkata, India were assessed for their suitability for the study. We recruited patients with either haemorrhagic or ischemic hemiparetic stroke with residual upper limb weakness at six months or later from stroke onset. Patients were excluded if they had any form of aphasia, frank dementia, hearing or visual impairment, had stroke in the pontomedullary region, received electrical stimulation as part of their physical therapy, or had fixed flexor deformities of the wrist joint.

A total of 95 patients were recruited. All continued to receive standard treatment; they were randomised to receive one of three interventions: Paired Stimulation Group, wearable device delivering clicks and shocks paired at a fixed interval; Random Stimulation Group, wearable device delivering clicks and shocks at the same rate, but at random with respect to each other; Standard Treatment Group, no device. The protocol was approved by the Institutional Ethics Committee (reference number INK/EthicsComm/46/2016 dated 2nd April 2016) and written informed consent was taken. The protocol was registered with the Clinical Trial Registry of India (CTRI/2018/03/012628).

Assessments

The outcomes were assessed at baseline (day 0, prior to randomisation to group), week 2, week 4 and week 8 by a blinded assessor, separate from the study team member who dispensed the device to the patients. All assessments were performed by a single assessor (SC) throughout the study.

The primary outcome measure was the Action Research Arm Test (ARAT) for estimation of upper limb function[15]. This is a summated rating scale with four domains – grasp, grip, pinch and gross. Scoring was based on the performance of a number of tasks from each domain. Each task was rated from 0 to 3, where higher scores denote less disability. There are 19 items in the scale, giving a maximum possible score of 57.

The tone of the forearm flexor group of muscles during passive extension of the wrist was assessed using the modified Ashworth scale, which evaluates resistance to passive movement on a score from 0 to 4[16]. Increased scores indicate increased tone; although this can be due to

spasticity, dystonia, muscle shortening or joint contractions, after stroke spasticity is the major contributor.

The power and pinch grip strength were measured as the average of three measurements with electro-dynamometers (G200 and P200, Biometrics Ltd, Newport, UK) of both the affected and less affected upper limbs.

The active range of movement around the wrist joint was measured using an electro-goniometer (SG75, Biometrics Ltd, Newport, UK). The participants were requested maximally to extend and then flex their wrist from their neutral position, yielding measures of maximum active extension and flexion and total range of movement at the wrist.

Maximum contraction force about the wrist joint was measured using a custom device. Patients sat comfortably in a fixed chair, with the forearm and wrist mid-pronated, the hand clamped between two vertical plates and the forearm strapped to a cushioned cast. The elbow was held at around 90° of flexion and the shoulder in approximately 30° of abduction. A strain gauge measured torque in the direction of wrist flexion-extension, about an axis concentric with the wrist joint. Subjects were asked to make maximal contractions in flexion and extension three times and the maximum values were analysed.

Signals from power/pinch dynamometers, the goniometer and the wrist strain gauge were digitised (power 1401 interface running Spike2 software, Cambridge Electronic Design, Cambridge, UK) and stored to hard disc for subsequent off-line analysis.

The subjective feeling of satisfaction of the patient after using the device was estimated by a five-point Likert scale (very satisfied to very dissatisfied).

Study procedure

After taking consent and completing the baseline (week 0) assessment, subjects were randomised to one of the three groups. Randomisation was performed using a customised MATLAB programme. When the sequentially-assigned subject number was inputted, the program reported whether the subject was to be issued a device (Paired Stimulation Group or Random Stimulation Group) or not (Standard Treatment Group). For the Paired or Random Stimulation Groups, the program then generated a coded file which was copied to a microSD card and inserted into the device before issue. This instructed the device how to configure the stimulation. Randomisation and issuing of the devices was performed by a member of the team who was not involved in assessments; this person also fielded any telephone queries from the

patients about device function. Patients were instructed not to discuss their device with those carrying out assessments. These procedures meant that all team members and the patients were blinded to whether patients issued with devices were in Paired or Random Stimulation Groups. Those carrying out assessments were completely blind as to group allocation. Randomisation was performed block wise: for every three sequentially-recruited patients, one was assigned to each group.

Paired and Random Stimulation Groups were instructed to use the device over four weeks for at least 4 hours per day at home from the first day of assessment (see flowchart). Patients were told not to use the device when taking a shower or while sleeping, but were otherwise free to use it for more than 4 hours per day if they wished. The patients were on stable doses of medication and physical therapy from 15 days prior to the baseline visit until the end of the study visits. They were instructed immediately to report any medical occurrence during the study period. All adverse events were recorded and treated appropriately and further assessed for causality.

Investigational Device

The device comprised a plastic box (90×60×20mm; see Fig. 1A) containing an electrical stimulator (constant current, 220V compliance) and audio amplifier. An inbuilt microprocessor read the SD card to determine whether to deliver paired or random stimulation, and also wrote files to the SD card logging the number of stimuli given in each session. The device was powered by an internal battery which could be recharged via a standard microUSB port. Cables led from the device to a miniature earphone which delivered loud clicks (0.1 ms pulse duration; intensity 110 dB SPL as in our previous study, which should be consulted for safety calculations[17]) to the ear contralateral to the affected side, and to a pair of adhesive surface electrodes (Kendall H34SG) placed over the forearm extensor muscles for transcutaneous electrical stimulation (single 0.15 ms pulse, proximal electrode negative[17]) . The patients and/or their immediate family members were trained regarding the placement of electrodes until they were confident in achieving reproducible positioning. To ensure patients/carers were continuing to place electrodes accurately, this training process was repeated at each visit. A knob on the device allowed adjustment of stimulus intensity; patients were told to increase the intensity until there was a just-visible extension of the wrist and/or fingers. Stimuli were given with an inter-stimulus interval randomly chosen (uniform distribution) from 1250-1750ms. For the Paired Stimulation Group, each shock was given 12ms before the click. For the Random

Stimulation Group, the click and shock occurred independently at random with the same interval distribution as in the Paired Stimulation Group.

Statistical Analysis

During study design, limited data were available to perform a power calculation to determine optimal sample size. Therefore, 95 consecutive patients were recruited over one year and seven months. Measurements from digitised force and wrist angle signals were made using custom MATLAB programs. Numerical data were presented as mean and standard deviation (for parametric data) or median and inter quartile range (for non-parametric data). Categorical data were presented as percentages. Normality was assessed by one sample K-S test and visual inspection of the distribution histogram and Q-Q plot, and parametric or non-parametric tests selected accordingly. For comparing two groups, we used unpaired t-tests for parametric data and Mann Whitney U tests for non-parametric data. The non-parametric data of more than two time points for the same patients were compared using Friedman's ANOVA with post hoc Dunn's tests. The difference between two or more rates/proportions was compared using Fisher's exact test. The correlation between two numerical variables was assessed by Spearman's correlation coefficient (ρ). All participants who completed at least one follow-up visit were included for analysis. 'Intention-to-treat' analysis was used. However, missing data due to dropout of subjects were not replaced by 'last observed outcome'. The statistical analysis was performed using SPSS version 20 (IBM Corporation).

Results

The demographic and disease characteristics of the 95 recruited patients are presented in Table 1. Factors likely to influence motor recovery after stroke were comparable among the three randomised groups. There was no significant difference in the total ARAT score across the three groups at baseline (median in Paired Stimulation, Random Stimulation and Standard Treatment Groups 7.5, 5 and 7 respectively; $p=0.194$). There was no significant difference between the number of stimuli given in the Paired Stimulation or Random Stimulation Groups (292 ± 149 versus 243 ± 146 thousand stimuli respectively, mean $\pm$ SD, $p=0.251$).

The Paired Stimulation Group showed a significant effect of visit number on total ARAT score ($p=0.019$); post-hoc pairwise testing showed an improvement from visit 1 to both visits 3 and 4 (median ARAT 7.5, 12.5 and 11.5 respectively; $p=0.012$ and $p=0.023$; Kendall's W for visit number, used as an estimate of effect size, 0.15). The Random Stimulation and Standard Treatment Groups showed no effect of visit number on the total ARAT scores (see Table 2).

The above analysis reports changes at a population level; it was also of interest to look at how many individual patients showed an improvement. We defined 'responders' as patients with at least a six-point increase in the total ARAT score (~10% of maximum). Seven patients (29%) from the Paired Stimulation Group compared with one (4%) of each of the other two groups were responders at visit 3; these proportions were significantly different (p=0.015). The response persisted at visit 4 in 5/7 responders from the Paired Stimulation Group.

The grasp sub-score improved significantly only in the Paired Stimulation Group. The grip, pinch and gross sub-scores did not show any significant change in any of the study groups (Table 2). Other outcome parameters (modified Ashworth score, isometric grip and wrist strength, angular movement around the wrist) did not show significant changes in any group.

Age, sex, duration since onset of stroke, type of stroke (haemorrhagic/ischaemic infarction), affected side (left/right), median baseline ARAT total score and sub-scores were not significantly different between responders and non-responders, as classified using visit 3 scores. The total number of paired stimuli received over the four weeks of device usage was significantly correlated with the change in ARAT score at visit 3 (Spearman's ρ=0.53, p=0.013) but not at visit 4 (ρ=0.285, p=0.223). There was no correlation between the number of stimuli received in the Random Stimulation group and ARAT change (Spearman's ρ= -0.052, p=0.814 and ρ=0.053, p=0.835 for visits 3 and 4 respectively).

Trial participants reported that stimulation did not interfere with or interrupt their normal activities of daily living, which typically involved light household work or leisure activities. Only one patient experienced a device-related adverse event. This individual developed a contact dermatitis where the adhesive electrodes had been placed. This improved with topical steroid, and did not have an impact on the experimental intervention as electrodes could easily be relocated to avoid the skin lesion. All patients successfully used the prototype device, although the study identified that the microUSB charge point was weak and prone to breakage (four devices over the entire study duration). Two patients disliked the repeated click sound and withdrew from the study at visit 2. Forty seven patients out of 64 (73%) who received a device intervention were either very satisfied or satisfied with the intervention. Out of 22 patients who withdrew from the study by visit 3 (device users), the majority (14) did so because of the burden of long-distance travel to our hospital from their place of residence.

Discussion

In this clinical trial, we observed that the Paired Stimulation Group demonstrated a small but statistically significant improvement of upper limb function over the four weeks of device usage, which was retained for at least four weeks after device stimulation ceased. Within this group, the extent of functional gain was correlated with stimulus number: those patients who chose to use the stimulation device for longer each day had better functional improvement. By contrast, patients allocated to the control groups (Random Simulation or Standard Treatment) did not show a significant improvement, suggesting that the benefit results specifically from paired stimulation.

Various neuromuscular stimulation modalities have been previously used for upper and lower limb motor recovery after stroke[18-20]. Either these devices are used to enhance a weak voluntary movement (functional electrical stimulation)[21] or stimulate muscles in the absence of any simultaneous effort from the patient[22]. These devices have found to be useful in the majority of clinical trials, although the improvement is usually only apparent during the spontaneous recovery phase[23,24].

Loud sound is known to be capable of activating not just the cochlea, but also the vestibular system; muscle responses to loud clicks are employed routinely for the assessment of the functional integrity of vestibular pathways (vestibular evoked myogenic potentials, see [25]). Previous work has shown that vestibular rehabilitation[26-29], rhythmic auditory stimulation[30] and music therapy[31] can all improve gait in stroke survivors. Extra-pyramidal pathways such as the vestibulospinal and reticulospinal tract receive strong vestibular and auditory inputs, and are intimately associated with the control of posture and locomotion; a contribution from the brainstem to recovery of gait might therefore be expected. However, we have shown that the reticulospinal tract also contributes to recovery of upper limb function after corticospinal tract damage[32-34]. To date, no studies have considered whether vestibular or auditory stimuli might improve rehabilitation of hand movements. Loud clicks can powerfully activate reticulospinal cells[12], and pairing clicks with peripheral stimuli can induce long-lasting changes in motor output consistent with spike-timing dependent plasticity[17]. These two observations led us to the present trial, which represents a novel and unique approach to stimulation-based therapy.

Our randomised, observer-blind clinical trial demonstrated a significant improvement in total ARAT score and the grasp sub-score following paired click and shock stimulation. This represents high quality evidence of a benefit at a population level, but on average the changes

were small (5 point median change in ARAT). In a chronic hemiparetic population, the 'patient-perceived minimal clinically important improvement' has been estimated as 5.7 points[35] (10% of the maximum possible ARAT score). However, here there was considerable inter-individual variation in the extent of improvement. Better outcomes were associated with higher baseline grip strength in the affected hand, and also with using the stimulation device for longer each day, thereby delivering more paired stimuli. Thus, when deciding whether to use our device for treatment, patients and their caregivers should be informed that only a sub-set of individuals with specific baseline characteristics demonstrated a significant outcome following four weeks of treatment. Future trials must address whether longer durations of device intervention beyond the minimum 4 hours per day for 4 weeks tested here could extend functional benefits to a wider group of patients. It would also be of interest to combine this protocol with other stimulation paradigms which may access different pathways[36,37], as this could allow synergistic gains in function.

Recent work in spinal cord injury survivors suggests that high spasticity is associated with limited residual corticospinal connections, and enhanced reticulospinal output below the lesion[38,39]; this accords with clinical experience associating spasticity with the reticulospinal tract[40]. Against this background, it might be thought that our intervention, which aimed to strengthen reticulospinal outputs, could have risked increasing spasticity. Reassuringly, our results yielded no evidence of increases in spasticity as measured by the Modified Ashworth Score.

There is evidence that spontaneous recovery of hand function after stroke relies on two separable systems: one provides strength and a limited degree of digit fractionation, whilst the other adds further ability to generate independent finger movements[41]. The system mainly responsible for strength recovery may be associated with the reticulospinal tract. This would agree with a recent study in our laboratory, where we have revealed a reticulospinal contribution to neural adaptations following strength training in healthy monkeys (IS Glover & SN Baker, unpublished observations). Despite this, in the present work we found no change in grip or wrist strength in the Paired Stimulation Group.

It is possible that the paired click and shock stimulation exerted its effects on systems other than the reticulospinal tract; this could explain why we observed no change in spasticity or strength. However, it is likely that the reticulospinal tract has multiple subdivisions, based on the reticular nucleus of origin[42] and the laterality of both projections to the cord, and control

from the cortex[43]. This richness probably explains why enhanced reticulospinal outputs have been associated by different authors with both recovery[33,34,44] and poor outcomes[11,45]. It is possible that the paired stimulation used here accessed only a sub-set of reticulospinal outputs, yielding an overall positive benefit to hand function. It is also possible that changes were too small to generate overt increases in strength, but still sufficient to yield improved control and enhanced ARAT scores.

Examination of the sub-components of the ARAT test showed a significant improvement in Grasp, but not in Grip, Pinch or Gross sub-scores. An improvement in hand movements requiring less well-fractionated muscle activation (Grasp) rather than fine independent finger movements (Grip, Pinch) would be compatible with a contribution from the reticulospinal rather than corticospinal tracts[46,47]. The lack of effect on the Gross subscore may reflect the fact that we targeted a forearm extensor muscle for stimulation, rather than more proximal muscles. Spontaneous recovery of hand function after stroke is typically imbalanced. Whereas wrist and digit flexors often regain strength the extensors remain weak, contributing substantially to disability[48]. This mirrors the pattern of spontaneous changes in reticulospinal connections after corticospinal lesions in monkey: outputs are strengthened to flexors but not to extensors[33]. We recently found that some forms of paired-associative stimulation showed a similar bias in their ability to induce plasticity in the corticospinal tract. No matter whether flexors or extensor muscles were stimulated, outputs were enhanced to flexors, but not extensors[37]. Although we targeted the forearm extensor muscles in the present trial, we found no change in isometric wrist extension strength in any group. Likewise, there was no change in active range of movement around the wrist, which is most affected in stroke survivors by extensor weakness. This may indicate that, just like the corticospinal tract, the reticulospinal tract has only a limited ability for stimulus-induced plasticity in output to extensors. The fact that there was, nevertheless, an average improvement in hand function hints at a complex reorganisation of control pathways, rather than a simple enhancement of one component.

One limitation of our study design was that we could not standardise the physical therapy program across patients. Many patients were receiving little or no physical therapy. However, there were no inter-group differences in the frequency or duration of physical therapy, suggesting that this could not have affected our results. We would expect even greater functional gains if the stimulation device was used concomitantly with a customised therapy regime, ideally at high dosage[49]. In this trial we targeted chronic stroke patients, to avoid the difficulty of trying to detect benefit against a moving baseline. The lack of significant changes

in the control groups confirmed that spontaneous recovery had indeed largely ceased. Stroke seems to generate a short-lived window of enhanced plasticity in the acute and sub-acute phase[50]. Using our paired stimulation device during this window might lead to even greater gains than we have seen in chronic patients, where plasticity has likely returned to baseline levels.

Acknowledgements

The authors wish to thank Norman Charlton and Felipe Carvalho for assistance in designing the wearable device used in this study, and Prof. Dr Robin Sengupta for his constant support.

Funding

Initial work on the wearable device was funded by Medical Research Council grant G0801705 and Wellcome Trust grant 101002 to SNB.

Disclosures

None.

References

1. Kamalakannan S, Gudlavalleti AS, Gudlavalleti VSM, Goenka S, Kuper H. Incidence & prevalence of stroke in India: A systematic review. *The Indian journal of medical research.* 2017;146(2):175.
2. Kwakkel G, Kollen BJ, Wagenaar RC. Therapy impact on functional recovery in stroke rehabilitation: a critical review of the literature. *Physiotherapy.* 1999;85(7):377-391.
3. Morris JH, van Wijck F, Joice S, Donaghy M. Predicting health related quality of life 6 months after stroke: the role of anxiety and upper limb dysfunction. *Disabil Rehabil.* 2013;35(4):291-299.
4. Kamalakannan S, Venkata MG, Prost A, et al. Rehabilitation needs of stroke survivors after discharge from hospital in India. *Arch Phys Med Rehabil.* 2016;97(9):1526-1532. e1529.
5. Rodgers H, Shaw L, Cant R, et al. Evaluating an extended rehabilitation service for stroke patients (EXTRAS): study protocol for a randomised controlled trial. *Trials.* 2015;16(1):205.
6. McKevitt C, Fudge N, Redfern J, Sheldenkar A, Crichton S, Wolfe C. UK stroke survivor needs survey. *London: The Stroke Association.* 2010.
7. Baker SN. The primate reticulospinal tract, hand function and functional recovery. *J Physiol.* 2011;589(Pt 23):5603-5612.

8. Baker SN, Zaaimi B, Fisher KM, Edgley SA, Soteropoulos DS. Pathways mediating functional recovery. *Progress in Brain Research.* 2015;218:389-412.
9. Choudhury S, Shobhana A, Singh R, et al. The Relationship Between Enhanced Reticulospinal Outflow and Upper Limb Function in Chronic Stroke Patients. *Neurorehabil Neural Repair.* 2019;33(5):375-383.
10. Zaaimi B, Edgley SA, Soteropoulos DS, Baker SN. Changes in descending motor pathway connectivity after corticospinal tract lesion in macaque monkey. *Brain.* 2012;135(7):2277-2289.
11. McPherson JG, Chen A, Ellis MD, Yao J, Heckman CJ, Dewald JPA. Progressive recruitment of contralesional cortico-reticulospinal pathways drives motor impairment post stroke. *J Physiol.* 2018;596:211-1225.
12. Fisher KM, Zaaimi B, Baker SN. Reticular formation responses to magnetic brain stimulation of primary motor cortex. *J Physiol.* 2012;590(Pt 16):4045-4060.
13. Foysal KR, de Carvalho F, Baker SN. Spike timing-dependent plasticity in the long-latency stretch reflex following paired stimulation from a wearable electronic device. *J Neurosci.* 2016;36(42):10823-10830.
14. Bi G, Poo M. Synaptic modification by correlated activity: Hebb's postulate revisited. *Annu Rev Neurosci.* 2001;24:139-166.
15. McDonnell M. Action research arm test. *Aust J Physiother.* 2008;54(3):220.
16. Pandyan A, Johnson G, Price C, Curless R, Barnes M, Rodgers H. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. *Clin Rehabil.* 1999;13(5):373-383.
17. Foysal KHMR, De Carvalho F, Baker SN. Spike-timing dependent plasticity in the long latency stretch reflex following paired stimulation from a wearable electronic device. *Journal of Neuroscience.* 2016;36:10823–10830.
18. De Kroon J, Van der Lee J, IJzerman MJ, Lankhorst G. Therapeutic electrical stimulation to improve motor control and functional abilities of the upper extremity after stroke: a systematic review. *Clin Rehabil.* 2002;16(4):350-360.
19. Chae J, Sheffler L, Knutson J. Neuromuscular electrical stimulation for motor restoration in hemiplegia. *Top Stroke Rehabil.* 2008;15(5):412-426.
20. Takeda K, Tanino G, Miyasaka H. Review of devices used in neuromuscular electrical stimulation for stroke rehabilitation. *Medical devices (Auckland, NZ).* 2017;10:207.
21. Shindo K, Fujiwara T, Hara J, et al. Effectiveness of hybrid assistive neuromuscular dynamic stimulation therapy in patients with subacute stroke: a randomized controlled pilot trial. *Neurorehabil Neural Repair.* 2011;25(9):830-837.
22. Alon G, Levitt AF, McCarthy PA. Functional electrical stimulation enhancement of upper extremity functional recovery during stroke rehabilitation: a pilot study. *Neurorehabil Neural Repair.* 2007;21(3):207-215.
23. Powell J, Pandyan AD, Granat M, Cameron M, Stott DJ. Electrical stimulation of wrist extensors in poststroke hemiplegia. *Stroke.* 1999;30(7):1384-1389.
24. Chae J, Bethoux F, Bohinc T, Dobos L, Davis T, Friedl A. Neuromuscular stimulation for upper extremity motor and functional recovery in acute hemiplegia. *Stroke.* 1998;29(5):975-979.
25. Rosengren S, Welgampola M, Colebatch J. Vestibular evoked myogenic potentials: past, present and future. *Clin Neurophysiol.* 2010;121(5):636-651.
26. Mainka S, Wissel J, Völler H, Evers S. The use of rhythmic auditory stimulation to optimize treadmill training for stroke patients: a randomized controlled trial. *Front Neurol.* 2018;9.

27. Lee S, Lee K, Song C. Gait Training with Bilateral Rhythmic Auditory Stimulation in Stroke Patients: A Randomized Controlled Trial. *Brain sciences.* 2018;8(9):164.
28. Mulavara AP, Kofman IS, De Dios YE, et al. Using low levels of stochastic vestibular stimulation to improve locomotor stability. *Front Syst Neurosci.* 2015;9:117.
29. Fitzpatrick RC, Wardman DL, Taylor JL. Effects of galvanic vestibular stimulation during human walking. *The Journal of Physiology.* 1999;517(3):931-939.
30. Suh JH, Han SJ, Jeon SY, et al. Effect of rhythmic auditory stimulation on gait and balance in hemiplegic stroke patients. *NeuroRehabilitation.* 2014;34(1):193-199.
31. Johansson BB. Multisensory stimulation in stroke rehabilitation. *Front Hum Neurosci.* 2012;6:60.
32. Baker SN. The primate reticulospinal tract, hand function and functional recovery. *The Journal of physiology.* 2011;589(23):5603-5612.
33. Zaaimi B, Edgley SA, Soteropoulos DS, Baker SN. Changes in descending motor pathway connectivity after corticospinal tract lesion in macaque monkey. *Brain.* 2012;135(Pt 7):2277-2289.
34. Zaaimi B, Soteropoulos DS, Fisher KM, Riddle CN, Baker SN. Classification of Neurons in the Primate Reticular Formation and Changes After Recovery From Pyramidal Tract Lesion. *Journal of Neuroscience.* 2018;38:6190–6206.
35. Van der Lee JH, De Groot V, Beckerman H, Wagenaar RC, Lankhorst GJ, Bouter LM. The intra-and interrater reliability of the action research arm test: a practical test of upper extremity function in patients with stroke. *Arch Phys Med Rehabil.* 2001;82(1):14-19.
36. Bunday KL, Urbin MA, Perez MA. Potentiating paired corticospinal-motoneuronal plasticity after spinal cord injury. *Brain Stimul.* 2018;11(5):1083-1092.
37. Foysal KMR, Baker SN. A Hierarchy of corticospinal plasticity in human hand and forearm muscles. *J Physiol.* 2019;597:2729-2739.
38. Sangari S, Lundell H, Kirshblum S, Perez MA. Residual descending motor pathways influence spasticity after spinal cord injury. *Ann Neurol.* 2019;86(1):28-41.
39. Sangari S, Perez MA. Imbalanced Corticospinal and Reticulospinal Contributions to Spasticity in Humans with Spinal Cord Injury. *Journal of Neuroscience.* 2019;In Press.
40. Brown P. Pathophysiology of spasticity. *J Neurol Neurosurg Psychiatry.* 1994;57(7):773-777.
41. Xu J, Ejaz N, Hertler B, et al. Separable systems for recovery of finger strength and control after stroke. *J Neurophysiol.* 2017;118(2):1151-1163.
42. Sakai ST, Davidson AG, Buford JA. Reticulospinal neurons in the pontomedullary reticular formation of the monkey (Macaca fascicularis). *Neuroscience.* 2009;163(4):1158-1170.
43. Fregosi M, Contestabile A, Hamadjida A, Rouiller EM. Corticobulbar projections from distinct motor cortical areas to the reticular formation in macaque monkeys. *Eur J Neurosci.* 2017;45(11):1379-1395.
44. Ballermann M, Fouad K. Spontaneous locomotor recovery in spinal cord injured rats is accompanied by anatomical plasticity of reticulospinal fibers. *Eur J Neurosci.* 2006;23:1988-1996.
45. Karbasforoushan H, Cohen-Adad J, Dewald JPA. Brainstem and spinal cord MRI identifies altered sensorimotor pathways post-stroke. *Nature communications.* 2019;10(1):3524.
46. Zaaimi B, Dean LR, Baker SN. Different contributions of primary motor cortex, reticular formation and spinal cord to fractionated muscle activation. *Journal of Neurophysiology.* 2018;119:235-250.

47. Tazoe T, Perez MA. Cortical and reticular contributions to human precision and power grip. *J Physiol.* 2017;595(8):2715-2730.
48. Kamper DG, Harvey RL, Suresh S, Rymer WZ. Relative contributions of neural mechanisms versus muscle mechanics in promoting finger extension deficits following stroke. *Muscle Nerve.* 2003;28(3):309-318.
49. Ward NS, Brander F, Kelly K. Intensive upper limb neurorehabilitation in chronic stroke: outcomes from the Queen Square programme. *J Neurol Neurosurg Psychiatry.* 2019;90(5):498-506.
50. Zeiler SR, Hubbard R, Gibson EM, et al. Paradoxical Motor Recovery From a First Stroke After Induction of a Second Stroke: Reopening a Postischemic Sensitive Period. *Neurorehabil Neural Repair.* 2016;30(8):794-800.

Table 1. Summary and inter-group comparison of demographic and baseline characteristics. The difference of numerical variables among three independent groups were estimated using one-way ANOVA for parametric data, Kruskal-Wallis H test for non-parametric data and categorical variables using Fisher's exact test. P value < 0.05 was considered statistically significant (*). MCA, ACA, PCA: Middle, Anterior and Posterior Cerebral Artery respectively.

	Paired	Random	Standard	P value
Age in years(SD)	51(12.1)	53(9.9)	53(10.6)	0.746
Male(%)	24(35.8)	25(37.3)	18(26.9)	0.191
Duration in months from onset of stroke(SD)	55(142)	43(94)	30(29)	0.630
Infarct(%)	19(59.4)	20(62.5)	19(61.3)	1.000
Stable dose of baclofen in mg(SD)	20.4(20.8)	15.6(12.1)	15.6(13.6)	0.474
Physiotherapy hours per week(SD)	4.2(2.6)	3.5(2.2)	6.1(3.7)	0.203
Mean ARAT at baseline(SD)	18.3(19.4)	10.8(12.3)	17.3(20.0)	0.194
Modified Ashworth score mean(SD) at baseline	1.5(0.8)	1.9(1.0)	2.1(1.2)	0.179

Mean power grip at baseline, affected as % of unaffected (SD)	28.9 (22.98)	22.7 (13.16)	30.28 (16.48)	0.216
Range of movement around wrist in degrees (SD)	48.4 (40.21)	30.23 (37.06)	42.82 (43.59)	0.315
MCA(%)	13(40.6)	16(50.0)	16(51.6)	0.884
ACA(%)	1(3.1)	1(3.1)	1(3.2)	
PCA(%)	3(9.4)	1(3.1)	1(3.2)	

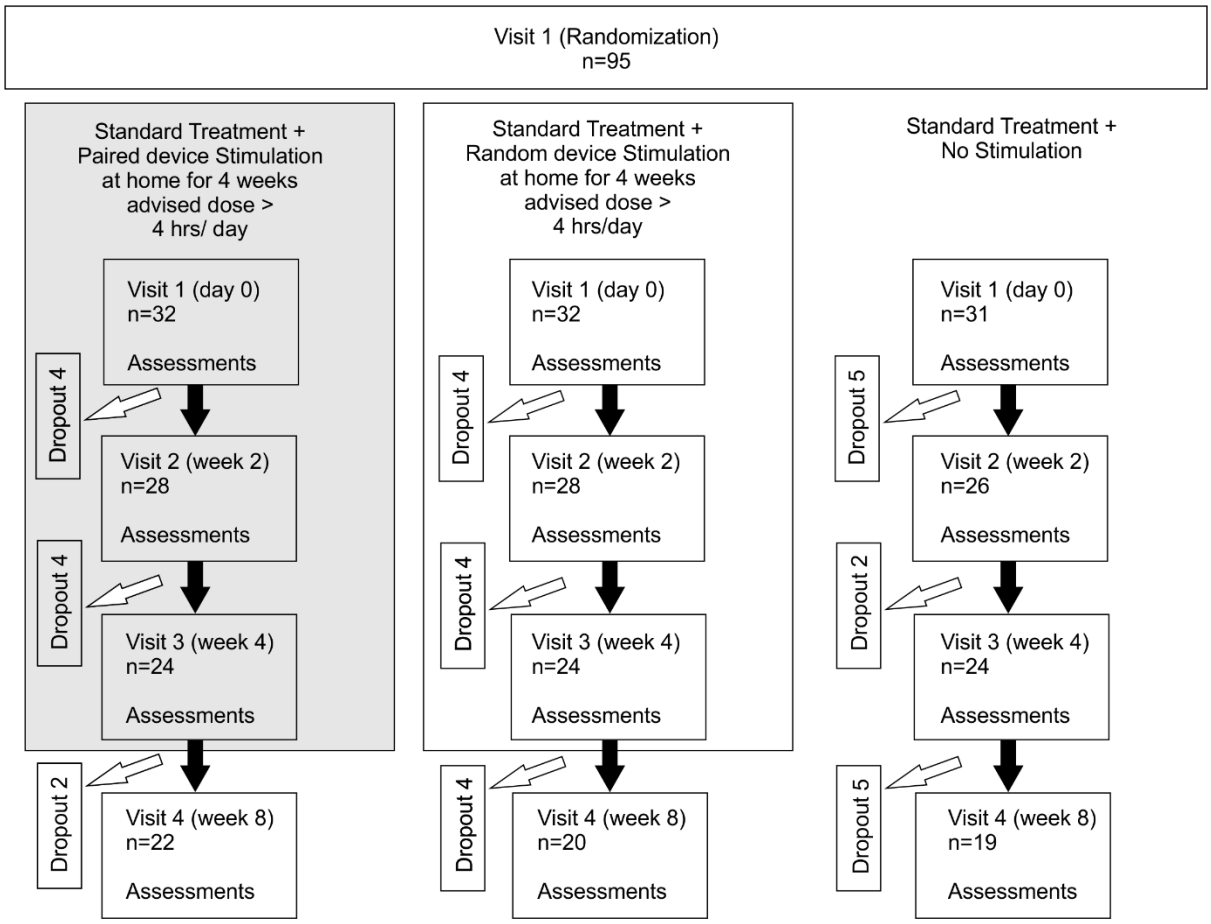
Table 2: Change in ARAT score and ARAT sub-scores over a period of 8 weeks. The difference of numerical variables expressed as median (interquartile range) in multiple time points for the same patients were estimated using Friedman's ANOVA. P value < 0.05 was considered statistically significant (*). Pairwise comparison was by *post hoc* Dunn's test with Friedman's ANOVA.

	V1-ARAT	V2-ARAT	V3-ARAT	V4-ARAT	P value
Paired	7.5(3.25-30.5)	11(5-38)	12.5(4.5-33.5)*	11.5(5-33.5)*	0.019*
Random	5(3-15)	6.5(4-20.75)	8.5(4-15)	7.5(0.25-18.75)	0.071
Standard	7(1-32)	10(1.5-24.75)	12(3-31)	9(0-21)	0.794
	V1-Grasp	V2-Grasp	V3-Grasp	V4-Grasp	P value
Paired	1(0-12)	3.5(0-14.25)	5(0-13.25)	4(0-14)*	0.004*
Random	1(0-8)	2(0-9.25)	2.5(0-6.75)	3(0-10)	0.079
Standard	1(0-11)	10(1.5-24.75)	4(0-11.75)	4(0-8.5)	0.479
	V1Grip	V2-Grip	V3-Grip	V4-Grip	P value
Paired	2(0-7)	3(1-7)	2.5(0.5-6.75)	3(0.75-14)	0.102
Random	0.5(0-3.75)	2(0-4.75)	2(0-4)	2(0-4)	0.247
Standard	2(0-6)	2.5(0-7)	3(0-7.75)	3.5(0-5.5)	0.923
	V1-pinch	V2-pinch	V3-pinch	V4-pinch	P value
Paired	0(0-8.25)	0(0-11.5)	0(0-9)	0(0-8.25)	0.055
Random	0(0-0)	0(0-1)	0(0-1)	0(0-1)	0.050

Standard	0(0-8)	0(0-2.75)	0(0-8)	0(0-1.25)	0.491
	V1-Gross	V2-Gross	V3-Gross	V4-Gross	P value
Paired	3.5(3-6)	4(3-7.75)	4(3-6.75)	3(3-4.75)	0.121
Random	3(3-5.5)	3.5(3-6)	4(3-5.75)	3(0-4)	0.215
Standard	4(0-6)	3.5(0-6)	3.5(3-6)	3.5(1.5-6)	0.324

Figure 1. The experimental device. A, photograph of the device, showing (from left to right): connector for stimulating electrodes; knob for adjusting stimulus intensity; audio output to earpiece; switch to select between 'on' and 'charge'; LED to indicate when battery is fully charged; microUSB connector for charger. B, device in use by a stroke patient in Kolkata as part of the trial to improve hand function.

Figure 2. Consort diagram indicating the progress of patients from recruitment to completion of the study. Assessments were - Action Research Arm Test; Modified Ashworth Scale; Range of Movement around wrist joint; Maximum wrist flexion/extension force; Power and pinch grip strength. n, sample size.



Supplementary table 1: Summary and inter-group comparison of ARAT scores in consecutive time points. The difference of numerical variables expressed as mean (standard deviation) and median (interquartile range) in multiple groups were estimated using Kruskal-Wallis ANOVA. P value < 0.05 was considered statistically significant.

Baseline ARAT				
	Paired	Random	Standard	P value
Mean	18.09	10.75	17.26	0.198
Median	7.500	5.000	7.000	
Std. Deviation	19.33	12.50	20.27	
25th percentile	3.250	3.000	1.000	
75th percentile	30.50	15.00	32.00	
Week 2 ARAT				
	Paired	Random	Standard	P value
Mean	20.79	13.29	16.50	0.299
Median	11.00	6.500	10.00	
Std. Deviation	20.39	13.76	19.19	
25th percentile	5.000	4.000	1.500	
75th percentile	38.00	20.75	24.75	
Week 4 ARAT				
	Paired	Random	Standard	P value
Mean	20.46	13.46	18.33	0.396
Median	12.50	8.500	12.00	
Std. Deviation	19.65	15.12	19.34	
25th percentile	4.500	4.000	3.000	
75th percentile	33.50	15.00	31.00	
Week 8 ARAT				
	Paired	Random	Standard	P value
Mean	19.77	12.00	14.42	0.310
Median	11.50	7.500	9.000	
Std. Deviation	19.00	14.17	16.38	
25th percentile	5.000	0.2500	0.000	
75th percentile	33.50	18.75	21.00	

Supplementary table 2: Summary and inter-group comparison of grasp sub-scores in consecutive time points. The difference of numerical variables expressed as mean (standard deviation) and median (interquartile range) in multiple groups were estimated using Kruskal-Wallis ANOVA. P value < 0.05 was considered statistically significant.

Baseline Grasp				
	Paired	Random	Standard	P value
Mean	5.844	3.531	5.452	0.709
Median	1.000	1.000	1.000	
Std. Deviation	7.030	4.879	6.707	

25th percentile	0.000	0.000	0.000	
75th percentile	12.00	8.000	11.00	
Week 2 Grasp				
	Paired	Random	Standard	P value
Mean	6.679	4.571	5.538	
Median	3.500	2.000	2.500	
Std. Deviation	7.409	5.718	6.730	0.795
25th percentile	0.000	0.000	0.000	
75th percentile	14.25	9.250	11.00	
Week 4 Grasp				
	Paired	Random	Standard	P value
Mean	6.875	4.542	6.208	
Median	5.000	2.500	4.000	
Std. Deviation	7.067	5.524	6.541	0.643
25th percentile	0.000	0.000	0.000	
75th percentile	13.25	6.750	11.75	
Week 8 Grasp				
	Paired	Random	Standard	P value
Mean	7.182	5.053	5.278	
Median	4.000	3.000	4.000	
Std. Deviation	7.228	5.602	5.809	0.652
25th percentile	0.000	0.000	0.000	
75th percentile	14.00	10.00	8.500	

Supplementary table 3: Summary and inter-group comparison of grip sub-scores in consecutive time points. The difference of numerical variables expressed as mean (standard deviation) and median (interquartile range) in multiple groups were estimated using Kruskal-Wallis ANOVA. P value < 0.05 was considered statistically significant.

Baseline Grip				
	Paired	Random	Standard	P value
Mean	4.063	2.219	3.742	
Median	2.000	0.5000	2.000	
Std. Deviation	4.265	2.992	4.531	0.222
25th percentile	0.000	0.000	0.000	
75th percentile	7.000	3.750	6.000	
Week 2 Grip				
	Paired	Random	Standard	P value
Mean	4.393	2.964	3.731	
Median	3.000	2.000	2.500	
Std. Deviation	4.280	3.109	4.387	0.510
25th percentile	1.000	0.000	0.000	

75th percentile	7.000	4.750	7.000	
Week 4 Grip				
	Paired	Random	Standard	P value
Mean	4.250	2.708	4.083	
Median	2.500	2.000	3.000	
Std. Deviation	4.173	3.099	4.413	0.484
25th percentile	0.5000	0.000	0.000	
75th percentile	6.750	4.000	7.750	
Week 8 Grip				
	Paired	Random	Standard	P value
Mean	4.455	2.947	3.722	
Median	3.000	2.000	3.500	
Std. Deviation	4.228	3.325	3.997	0.552
25th percentile	0.7500	0.000	0.000	
75th percentile	8.250	4.000	5.500	

Supplementary table 4: Summary and inter-group comparison of pinch sub-scores in consecutive time points. The difference of numerical variables expressed as mean (standard deviation) and median (interquartile range) in multiple groups were estimated using Kruskal-Wallis ANOVA. P value < 0.05 was considered statistically significant.

Baseline pinch				
	Paired	Random	Standard	P value
Mean	4.000	1.188	4.032	
Median	0.000	0.000	0.000	
Std. Deviation	6.263	3.780	7.007	0.179
25th percentile	0.000	0.000	0.000	
75th percentile	8.250	0.000	8.000	
Week 2 pinch				
	Paired	Random	Standard	P value
Mean	4.857	1.893	3.154	
Median	0.000	0.000	0.000	
Std. Deviation	7.096	4.573	6.123	0.250
25th percentile	0.000	0.000	0.000	
75th percentile	11.50	1.000	2.750	
Week 4 pinch				
	Paired	Random	Standard	P value
Mean	4.417	2.083	4.000	
Median	0.000	0.000	0.000	
Std. Deviation	6.921	5.141	6.897	0.628
25th percentile	0.000	0.000	0.000	
75th percentile	9.000	1.000	8.000	

Week 8 pinch				
	Paired	Random	Standard	P value
Mean	3.364	1.368	2.333	
Median	0.000	0.000	0.000	
Std. Deviation	6.268	4.112	5.258	0.985
25th percentile	0.000	0.000	0.000	
75th percentile	4.750	1.000	1.250	

Supplementary table 5: Summary and inter-group comparison of gross sub-scores in consecutive time points. The difference of numerical variables expressed as mean (standard deviation) and median (interquartile range) in multiple groups were estimated using Kruskal-Wallis ANOVA. P value < 0.05 was considered statistically significant.

Baseline gross				
	Paired	Random	Standard	P value
Mean	4.250	3.719	3.935	
Median	3.500	3.000	4.000	
Std. Deviation	2.615	2.020	3.183	0.826
25th percentile	3.000	3.000	0.000	
75th percentile	6.000	5.500	6.000	
Week 2 gross				
	Paired	Random	Standard	P value
Mean	4.857	4.214	3.808	
Median	4.000	3.500	3.500	
Std. Deviation	2.534	2.250	3.124	0.510
25th percentile	3.000	3.000	0.000	
75th percentile	7.750	6.000	6.000	
Week 4 gross				
	Paired	Random	Standard	P value
Mean	4.667	4.125	4.042	
Median	4.000	4.000	3.500	
Std. Deviation	2.200	2.213	2.805	0.786
25th percentile	3.000	3.000	3.000	
75th percentile	6.750	5.750	6.000	
Week 8 gross				
	Paired	Random	Standard	P value
Mean	4.773	3.263	3.889	
Median	3.000	3.000	3.500	
Std. Deviation	2.349	2.557	2.888	0.330
25th percentile	3.000	0.000	1.500	
75th percentile	7.250	4.000	6.000	